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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,589	06/08/2000	Katherine A. High	018743/0276324	1864

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/589,589	HIGH ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-8,10,12-21,23-25 and 28-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-8,10,12-21,23-25,28-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Final Rejection

Claims 1-4, 6-8, 10, 12-21, 23-25, and 28-40 are pending.

Applicants' traversal, the amendment to the claims 1, 6, 8, 12-14, 17, 18, and 25, the cancellation of claims 5 and 22, and the addition of claim 40 in paper filed on 5/10/04 is acknowledged and considered.

Election/Restrictions

The non-elected species in claims 16, 19, 32 and 37 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/15/01. NOTE: The statement "Applicant timely traversed the restriction (election) requirement in paper No. 11" in the non-final rejection mailed on 1/9/04 by the examiner was incorrect in view of the election without traverse in paper filed on 10/15/01 and the statement confirming the election without traverse in the paper mailed on 11/8/01.

Claim Objections

Claims 1, 6, 8, 12, 13, 14, 17, 18, and 25 are objected to because of the following informalities: In view of the revised amendment practice 37 CFR 1.121, the status of these claims is incorrect. The only status identifiers that should be used are: original, **currently amended**, canceled, withdrawn, new, previously presented and not entered. The amended claims should have should be identified as currently amended.

When filing the amendment to this instant action, applicants are reminded to follow the revised amendment practice 37 CFR 1.121. See 68 Fed. Reg. 38611 (June 30, 2003) or website http://www.uspto.gov/web/patents/ifw/.

Appropriate correction is required.

Applicants are advised that should claim 30 be found allowable, claim 33 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The limitation "an increase in Factor IX is observed in said mammal," in claim 30 is inherent in claim 33 because delivering Factor IX by way of gene therapy to a mammal would result in an increase in Factor IX observed in the said mammal.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 3, 4, 6, 10, 12, 13, 14, 15, 16, 19, 20, 28, 29, 30, 31, 32, 33, 35, 37, and 38 remain and claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al. (US 6,251,957) taken with Bach (WO 96/25177) in further view of Tripathy et al., (Nat. Med. 1996, 2:545-550).

Wilson teaches a gene therapy method comprising co-administering with a viral vector an immunosuppressive agent to a human (column 2, lines 35-52, column 4, lines 20-34 and column 25-26). Wilson teaches co-administering cyclophosphamide (column 5, line 52-column 6, line 23 and column 8, lines 34-45). Wilson teaches that the immunosuppressive agent may be administered prior to or concurrently with the recombinant viral vector (column 2, lines 45-49). Wilson teaches that an immune response can be the product of the transgene when that transgene expresses a protein that is foreign to the treated host (column 1, lines 63-65). However, Wilson

does not specifically teach using a viral vector comprising a nucleotide sequence encoding a blood coagulation protein and an immunosuppressive agent in a method of gene therapy in a mammal, wherein the delivered protein is the same species as said mammal.

However, at the time the invention was made, Bach teaches a method of combining an immunosuppressive agent and at least one adenovirus comprising a DNA containing a therapeutic gene (see abstract and page 3 of the US 2003/0004091, which is the English equivalent of WO 96/25177). Bach teaches that the invention makes it possible to achieve therapeutic effect, which is markedly prolonged (page 2 of the US 2003/0004091, which is the English equivalent of WO 96/25177). The DNA or therapeutic gene is from human (page 3 of the US 2003/0004091, which is the English equivalent of WO 96/25177). Bach teaches that the therapeutic gene can encode factors VII, VIII, and IX (page 3 of the US 2003/0004091, which is the English equivalent of WO 96/25177).

In addition, at the time the invention was made, Tripathy teaches that novel proteins delivered by way of gene therapy, including deficient human proteins in patients with recessive diseases generate immune responses (page 549).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wilson taken with Bach in further view of Tripathy to co-administer cyclophosphamide with a recombinant virus comprising a nucleotide sequence encoding a blood coagulation protein, e.g., Factor IX. One of ordinary skill in the art would have been motivated to combine the teaching because either Wilson or Bach teach that it is advantageous (prolonging therapeutic effect) to co-administer an immunosuppressive agent (e.g., cyclophosphamide) with a recombinant virus comprising a therapeutic gene. In addition,

one of ordinary skill in the art would have been motivated to co-administer an immunosuppressive regimen with gene therapy because Tripathy, Wilson, and Bach teach that exposure of a novel human protein by way of gene therapy to a human deficient for the protein results in an immune response against the protein. Furthermore, the method taught by Wilson taken with Bach in further view of Tripathy has the same limitations as the claimed method. The method taught by Wilson taken with Bach in further view of Tripathy uses the same material(s) and method(s). Therefore, absence evidence to the contrary, one of ordinary skill in the art would reasonably conclude that the method would result in preventing or inhibiting the formation of inhibitory antibodies to a blood coagulation protein delivered to a mammal by way of gene therapy.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 5/10/04 have been fully considered but they are not persuasive because one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. Applicants argue that Wilson, Bach or Tripathy do not teach or suggest an immune response is produced against the protein delivered by way of gene therapy, let alone an immune response against a protein that is the same species as the mammal to which is delivered. In view of the totality of the prior art and the reasons set forth above, one of ordinary skill in the art would have been motivated to practice the claimed method.

With respect to applicants' argument that there would be no reasonable expectation of success of producing the claimed methods in view of Wilson, Bach and Tripathy, the argument is not found persuasive because there is no evidence of record to support applicants' assertion. See MPEP § 716.01(c).

With respect to applicants' argument that Herzog Blood teaches away from the claimed methods, the argument is moot because Herzog was not cited in the rejection.

In response to applicants' argument that one skilled in the art would not have administered an immunosuppressive agent prior to or simultaneously with gene therapy when the gene delivered encodes a protein that is the same species as the mammal to which it is delivered, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). This is the case here. Wilson or Bach teach that it is advantageous (prolonging therapeutic effect) to co-administer an immunosuppressive agent (e.g., cyclophosphamide) with a recombinant virus comprising a therapeutic gene. Furthermore, the method taught by Wilson taken with Bach in further view of Tripathy uses the same material(s) and method(s). Therefore, absence evidence to the contrary, one of ordinary skill in the art would reasonably conclude that the method would result in preventing or inhibiting the formation of inhibitory antibodies to a blood coagulation protein delivered to a mammal by way of gene therapy.

With respect to applicants' argument that nowhere does Tripathy, Wilson, or Bach teach or suggest that an immune response is produced against a protein delivered by way of gene therapy when the protein is the same species as the mammal to which it is delivered, the

argument is not found persuasive because as stated by applicants Tripathy teaches delivering a murine EPO gene to mice (see page 11 of applicant's argument).

In addition, with respect to applicants' argument that in view of Tripathy the skilled artisan would not have administered an immunosuppressive agent prior to or simultaneously with gene therapy when the gene delivered encodes a protein that is the same species as the mammal to which it is delivered because to do so would be pointless, the argument is not found persuasive because the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). This is the case here. Wilson or Bach teach that it is advantageous (prolonging therapeutic effect) to co-administer an immunosuppressive agent (e.g., cyclophosphamide) with a recombinant virus comprising a therapeutic gene.

Claims 1, 12, 13, 14, 21, 23, 24, 25, and 39 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al. (US 6,251,957) taken with Bach (WO 96/25177) and Tripathy et al., (Nat. Med. 1996, 2:545-550) as applied to claims 1-4, 6, 10, 12-16, 19, 20, 28-33, 35, 37, 38 and 40 above, and further in view of Nilsson (PNAS, 83:9169-9173, 1986) and Warrier (Blood Coagul Fibrinolysis, 1998; 9 Suppl 1: S125-8).

The rejection of the base claims 1, 12, 13, and 14 under 35 U.S.C. 103(a) is applied here as indicated above, by Wilson taken with Bach in further view of Tripathy. However, Wilson, Bach and Tripathy do not specifically teach using the claimed method, wherein said mammal has

no detectable endogenous expression of the blood coagulation protein or said human has hemophilia B and said inhibitory antibodies bind specifically with Factor IX protein.

However, at the time the invention was made, Nilsson teaches a complication of Factor IX therapy is the development of antibodies to Factor IX (page 9169).

Furthermore, at the time the invention was made, Warrier teaches that the development of inhibitory antibodies is a serious complication of hemophilia in young children. Inhibitors are commonly associated with the total absence of FIX antigen due to total deletions or other major derangements of the FIX gene.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wilson taken with Bach and Tripathy in further view of Nilsson and Warrier to co-administer an immunosuppressive agent with a viral vector comprising a nucleotide sequence encoding a FIX protein. One of ordinary skill in the art would have been motivated to combine the teaching because Nilsson and Warrier teach that the major problem with Factor IX therapy is the development of antibodies to Factor IX. In addition, Bach and Wilson teach using combination therapy to solve the problem with the immune response to a transgene that is foreign to the treated host.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 5/10/04 have been fully considered but they are not persuasive because of the same reasons as set forth above in the prior 103(a) rejection and because one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208

USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. Applicants' argue that Nilsson does not even mentioned gene therapy. The claimed gene therapy method was already taught by Wilson, Bach and Tripathy, Nilsson was cited in the rejection to display that Factor IX therapy in hemophiliacs produce antibodies against Factor IX. With respect to Warrier, applicants argue that Warrier fails to teach or suggest using the claimed methods. As stated above, the claimed gene therapy method was already taught by Wilson, Bach and Tripathy and Warrier was cited to teach that due to total deletions or other major derangements of the FIX gene some hemophiliacs do not express endogenous factor IX.

Claims 1, 3, 6, 7, 8, 13, 14, 16, 33-36 remain and claims 17, 18, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al. (US 6,251,957) taken with Bach (WO 96/25177) and Tripathy et al., (Nat. Med. 1996, 2:545-550) as applied to claims 1-4, 6, 10, 12-16, 19, 20, 28-33, 35, 37, 38 and 40 above, and further in view of Herzog et al., (IDS, PNAS, vol. 94, pages 5804-5809, 1997).

The rejection of the base claims 1, 3, 6, 13, 14, 16, 33, 35, and 40 under 35 U.S.C. 103(a) is applied here as indicated above, by Wilson taken with Bach in further view of Tripathy. However, Wilson, Bach and Tripathy do not specifically teach using a recombinant adeno-associated viral vector (rAAV) in the claimed method.

However, at the time the invention was made, Herzog teaches that AAV viral vectors can be used to deliver therapeutic levels of FIX after intramuscular injection and can be used for treating patients with hemophilia B (page 5804).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wilson and Bach and Tripathy in further view of Herzog to use rAAV in the claimed methods. One of ordinary skill in the art would have been motivated to use rAAV in the claimed methods because Herzog teaches that AAV viral vectors can be used to deliver therapeutic levels of FIX after intramuscular injection and can be used for treating patients with hemophilia B.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 5/10/04 have been fully considered but they are not persuasive because of the same reasons as set forth above in the prior 103(a) rejections and because one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. Herzog is added to the 103(a) rejection over Wilson, Bach and Tripathy to teach using an AAV vector to deliver Factor IX to a mammal.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, SPE - Art Unit 1635, can be reached at (571) 272-0760.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

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